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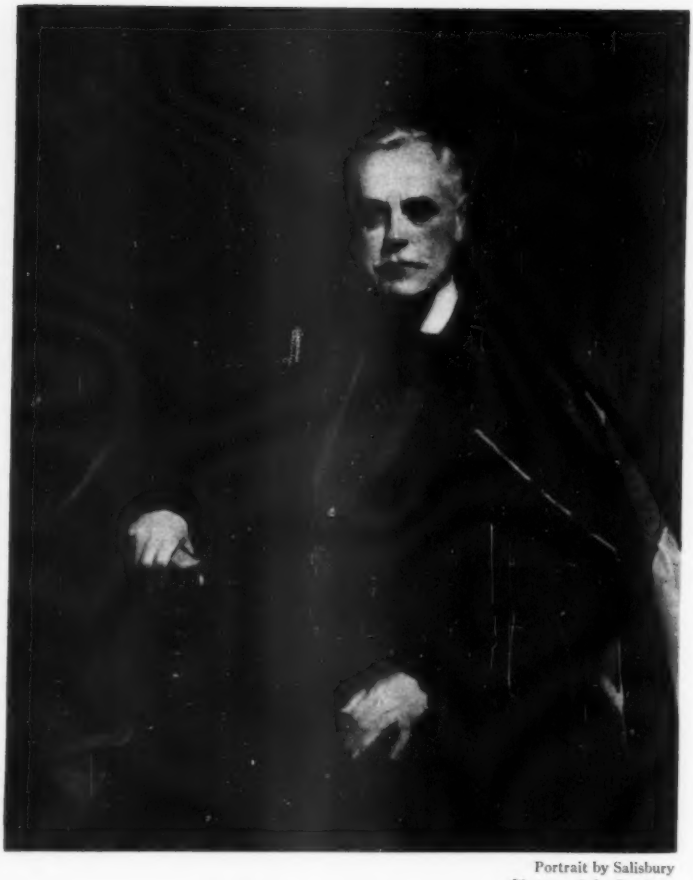

Portrait by Salisbury
Photograph by Bendann

WILLIAM HOLLAND WILMER

William Holland Wilmer
1863–1936

MINUTE ADOPTED BY THE ADVISORY BOARD OF THE MEDICAL FACULTY, MARCH 27, 1936

Moved: That the Advisory Board of the Medical Faculty, by this minute, record its deep sorrow over the death of a distinguished former member of the Board, Dr. William Holland Wilmer, Professor Emeritus of Ophthalmology in this University and Director Emeritus of the Wilmer Ophthalmological Institute.

A native of Virginia and a graduate of the University of that state, Dr. Wilmer, after a special training in ophthalmology in New York, began the practice of that specialty in Washington in 1889. His development was rapid and he soon became one of the leaders in that field. This leadership was based upon a firm understanding of the fundamentals of his subject, a clear recognition of the relationship of ocular disease to general systemic disease, exceptional diagnostic and surgical skill, and above and beyond these a remarkable sympathy for his patients and a deep understanding of their psychological needs. His personal charm and magnetism made themselves felt by patients, friends and colleagues alike, and had much to do with Dr. Wilmer's extraordinary success in the practice of his art.

The Advisory Board is well aware of Dr. Wilmer's services to the country during the World War as well as the other contributions which he made prior to his coming to Baltimore, but above these it would emphasize the contribution which he made as a member of the Johns Hopkins University and of the Johns Hopkins Hospital. Here he established upon a firm clinical foundation the first University clinic in Ophthalmology in America, a University clinic in every sense of the word, where teaching and research should go hand-in-hand with the care of patients.

The planning and launching of this enterprise constituted the supreme achievement of his life, and the ideals of the Institute which he founded, together with the men whom he trained, will probably form

his most enduring memorial. His colleagues of the Johns Hopkins University revere his memory not only for this achievement, but for his own scientific attainments, his personal magnetism, his kindliness and his friendliness. They deeply regret the loss which the science of ophthalmology and this University have sustained in his death, and they take comfort only in the fact that his final illness was extremely brief and that he was spared a long interval of pain and suffering.

DIFFERENTIAL DIAGNOSIS OF DISSEMINATED SCLEROSIS FROM OTHER FORMS OF MULTILOCULAR ENCEPHALOMYELOPATHY

Comments upon Recent Ideas Concerning Etiology and Treatment[1]

LEWELLYS F. BARKER, M.D.

Baltimore, Maryland

Submitted for publication April 3, 1936

As our knowledge of disorders of the central nervous system has increased, we have become acquainted with a number of diseases that are capable of causing multiple lesions within the brain and the spinal cord, so that the task of differential diagnosis of these multiple encephalomyelopathies falls to the lot of the clinical neurologist. In some cases it is relatively easy to be sure of the nature of the process concerned; in other cases, however, the difficulties of differentiation may be so great that the clinician has to be satisfied with a diagnosis that is only probable rather than certain.

The case reported here is one that, after due consideration of the symptoms and signs and the probable localization of the lesions, leaves but little doubt as to its nature; it gives opportunity, however, for a brief discussion of differential diagnosis in cases in which the nature of the process concerned is less obvious.

CASE HISTORY

James F., a white man, aged 27, entered the Osler Ward of the Johns Hopkins Hospital (Service of Professor Warfield T. Longcope) on January 24, 1936, complaining of weakness of the legs, disturbance of vision in the right eye, and numbness of fingers of the left hand.

Family history. The patient's father died at 35 of influenza. His mother is living and well at the age of 43. His parents had eight children, two dying in infancy, the others living and well. The father weighed 240 pounds at the time

[1] Clinic for the Senior Students of the Johns Hopkins Medical School, February 6, 1936.

of his death, but there is no history of any hereditary disease in the family nor of any one suffering from complaints similar to those of the patient.

Past history. The patient is a married man and his wife is now pregnant. Since the age of 14 he has been an industrial worker, holding jobs with different manufacturing companies, in none of which was he exposed to fumes or to heavy metals. For the past seven months he has been unemployed because of his present illness.

The patient says that he has always enjoyed very good health except for chickenpox and measles in childhood and two attacks of grippe during the past two years, in each of which there was an upper respiratory infection followed by chills, fever and general malaise. He has never suffered any trauma.

He was operated upon for tonsillitis and adenoids at the age of eight, and a second time in December of last year. At the age of ten he had earache with intermittent otorrhea lasting about a year. He has had several teeth extracted and others have been filled. The only venereal infection reported is a gonococcal attack about seven years ago. This was carefully treated at a local hospital.

As to his personal habits, he has been a cigarette smoker, sometimes smoking a pack a day, but since last autumn he has given up smoking entirely. He has used alcohol in moderation and only occasionally to excess. He has no drug habits.

Present illness. Some fourteen months ago he noticed peculiar prickling sensations ("pins and needles") in the left lower extremity and about three months later complained of weakness in the knees, and of blurring of vision of the right eye. A little later he observed that his balance was poor and that he had a tendency to stagger when walking. The left leg seemed to trouble him more than the right. He felt dizzy if his eyes were closed. Eight months ago he began to have itching, especially of the nose and face. His disabilities increased so much that seven months ago he was compelled to give up his job. About five months ago he noticed memory difficulties, not only memory for recent events but also for more remote experiences. His speech also became slowed up. He found difficulty in getting the word he wanted to say, and there was some slurring. The fingers of the left hand became numb and he had difficulty in buttoning and unbuttoning his clothes, and in lacing his shoes. He noticed that his left arm was somewhat clumsier than his right. Because of difficulties of vision he got glasses, but the blurring of the right eye still continued. He has had no headaches, but his sleep has been somewhat disturbed. He often wakes about midnight and finds it difficult to go to sleep again. He has had some difficulty in starting the flow of urine, which he speaks of as a "stuttering bladder" and the physician who examined him last year found the prostate somewhat enlarged. There has been no decrease of libido and potentia. He has had some gaseous indigestion and constipation, and has often used enemata during the past year. There has been no disturbance of the anal sphincter. He has been remarkably cheerful throughout his illness despite the fact that it has handicapped him.

Physical examination. On admission his temperature was 99°, the respiratory rate 16, pulse rate 80, blood pressure 125/78 in the right arm and 130/100 in the

left arm. Body well nourished but no marked obesity. Lips and mucous membranes of good color. No general glandular enlargement. Slight nasal obstruction, due to deviation of the septum. Lungs and heart negative. Liver and spleen not palpable.

Neurological examination. The patient is somewhat euphoric. There is some disturbance of recording faculty and of memory for recent and remote events, but there have been no hallucinations or delusions. His speech is slow with a tendency to scanning. He sometimes speaks a word loudly without meaning to do so. He can read and understand what he reads and understands everything that is said to him. He has had no difficulty in recognizing objects or their use. At times he has seen double. There is definite weakness of the muscles of the left lower extremity and of the pelvic girdle. Muscles of the trunk and arms seem to be strong. There is some horizontal nystagmus. The gait is disturbed. He cannot walk a line. There is some ataxia of the left hand with intention tremor of the fingers of that hand. The Romberg is definitely positive.

On the sensory side, in addition to the early paraesthesias of the lower extremities and the disturbance of vision in the right eye, he has developed anaesthesia of the left hand, loss of vibration sense, especially in the left lower extremity, and some vertigo. There is pallor of the whole of the right optic disc and of the temporal half of the left disc. The visual fields show scattered scotomata.

The deep reflexes are active in all four extremities. Babinski positive on the left and equivocal on the right. There is loss of both abdominal reflexes, though the cremaster reflexes are present.

In autonomic domains he has had a "stuttering" bladder, persistent constipation, a tendency to perspiration, and dermatographia.

Laboratory tests. Blood counts, including differential counts, have been quite normal. Wassermann reaction in the blood, negative.

No marked abnormalities in *urine* or *feces*.

The *cerebrospinal fluid* was found to be under normal pressure. Pandy reaction positive. Protein content 25 mgm. per cent. Cell count not increased. Wassermann reaction negative. Colloidal gold curve entirely negative (flat curve).

Localization of the neurological lesions. As to the lesions of *motor pathways*, the weakness in the lower extremities, especially the left, with the Babinski positive on the left and equivocal on the right, points to the pyramidal tracts of both sides; the speech disturbance points to lesions in the brain stem; and the spontaneous nystagmus to lesions of the vestibulo-ocular mechanism in the brain stem.

In *sensory domains*, the paraesthesias of the lower extremities point to irritation of the cutaneous sensory pathways in the cord or brain; the loss of vibration sense in the left lower extremity indicates involvement of the paths of tactile sensation, either in the cord or brain. The numbness of the left hand points to the sensory pathway in the lateral column of the cord; the disturbance of vision in the right eye with pallor of the whole of the right disc points to injury to the right optic nerve, whereas temporal pallor of the left disc suggests partial injury of the left

optic nerve (primary atrophy). The slight vertigo indicates disturbance of the vestibular apparatus; and the positive Romberg indicates injury to the spinocerebellar paths, probably in the posterior funiculi of the cord.

The loss of abdominal *reflexes* could be due either to injury of the spinal arc or of the upper cortical arc for these reflexes.

The transient diplopia is suggestive of injury to the fasciculus longitudinalis medialis (medial longitudinal bundle).

The "stuttering" bladder and the persistent constipation indicate either injury to the innervation of the voluntary sphincter of the bladder or to the involuntary activity of the bladder wall and to paresis of the wall of the bowel (in *autonomic domains*).

The memory disturbances point to the cerebral cortex. The euphoria indicates a brain disturbance; it is interesting that euphoria may occur in multilocular organic lesions of the brain, for example, in general paresis of the insane.

Nature of the neurological lesions. Inflammatory lesions seem improbable on account of the history of the development of the symptoms, the absence of pleocytosis in the cerebrospinal fluid, and the absence of leucocytosis in the blood; multiple lesions due to an *encephalomyelitis* of any sort, including *epidemic encephalitis*, would seem therefore very improbable, and *multiple luetic lesions* are ruled out by the negative Wassermann in both blood and spinal fluid.

Multiple neoplastic lesions would seem very improbable; there is no evidence of increased intracranial or of intraspinal pressure and there is no primary tumor demonstrable anywhere in the body.

When multiple sclerosis begins, as it sometimes does, with spastic paraplegia, it may be mistaken for *amyotrophic lateral sclerosis*, but the development of eye signs later and the absence of steady progression in the symptoms in multiple sclerosis help us to differentiate.

The onset in a young person under thirty years of age, the multiplicity of the symptoms, the primary optic atrophy, the pyramidal tract disturbances, the loss of abdominal reflexes, the nystagmus and the scanning speech, made the diagnosis of *disseminated sclerosis* seem unavoidable to Dr. Harvey and other members of the staff, and I agree with their conclusion. Though the symptoms complained of began only about one year ago, it is possible that, had the patient been examined earlier, certain symptoms and signs suggestive of the onset of multiple sclerosis, especially loss of abdominal reflexes and bitemporal pallor of the optic discs, might have been discovered.

In some cases of multiple sclerosis the ataxia is a dominant feature and neurologists have to rule out *Friedreich's ataxia*, on the one hand, and *Marie's hereditary ataxia*, on the other. The differentiation is usually easy, since there is a distinct familial history of these ataxias, the abdominal reflexes are usually preserved, the deep reflexes are generally diminished, and optic atrophy is usually absent.

In children, *Schilder's disease* (*encephalitis periaxialis diffusa*) may cause mental disturbances, ataxia, tremor and pyramidal tract lesions; the condition is, however, more acute and more rapidly fatal than is multiple sclerosis.

A mistake far too often made by practitioners on seeing a patient with multiple sclerosis in its early stages is to assume that the symptoms are due to *hysteria*; the phenomena observed are thought to be of functional origin, especially when the disease undergoes a marked remission. In many instances in which a diagnosis of hysterical amaurosis or of functional hysterical dysbasia has been made, a more careful study would have shown the organic nature of the process. The loss of the abdominal reflexes, the pallor of the optic discs (especially on the temporal side), the slight objective disturbances in sensibility and a history of diplopia and of mild bladder disturbances would be given due consideration.

ETIOLOGY OF MULTIPLE SCLEROSIS

Concerning the cause of disseminated sclerosis nothing reliable is as yet known. Relations to preceding infections, intoxications or traumata have not been established, though it is of course admitted that when the disease exists such factors may cause exacerbation. Since 1917, especially through Kuhn and Steiner, the attempt has been made to relate disseminated sclerosis to a spirochaetal infection. Though occasionally spirochaetes seem to have been found in fresh tissues at autopsy, the majority of investigators agree that the finding is by no means constant.

Another hypothesis has been promulgated, namely, that disseminated sclerosis may represent a "metatuberculous" disease of the nervous system in the sense that dementia paralytica and tabes dorsalis were formerly thought of as "metasyphilitic" diseases of that system. The hypothesis would seem to be without merit.

Recently, Putnam and his associates in Boston have suggested that minute venous thromboses are the starting point of the lesions in the nervous system in disseminated sclerosis and that these thromboses may depend in turn upon abnormalities in the coagulability of the blood which, it is asserted, may be regularly observed in multiple sclerosis (Solomon and Simon). This hypothesis meets with two especial difficulties: (1) Granting abnormal coagulability of the blood, why should thrombi occur in venules in the nervous system rather than elsewhere? and (2) What is the origin and nature of the reported changes in blood coagulability?

THE HISTOPATHOLOGY OF MULTIPLE SCLEROSIS

It has long been known that in the early lesions of multiple sclerosis the myelin sheaths of the nerve fibres are injured to a far greater

extent than the axones, and the disease evidently falls in the group of "demyelinization processes" of which Schilder's disease (encephalitis periaxialis diffusa) is another member. Straussler and Scheinker have described a peculiar spongy structure of the sclerotic areas. The group of diseases in which there is outspoken demyelinization with relative preservation of axis cylinders has been studied especially by Hallervorder and Spatz.

Attempts to produce lesions similar to the early changes in multiple sclerosis have been made experimentally in animals by injection of minute doses of tetanus toxin or by obstruction of venules in the dog's brain with a bland oil (Putnam and his associates). Following these experiments, at first a diffuse proliferation of fixed glia cells and mild myelin damage were found, but at the end of three months myelin destruction had begun and after ten months there was a dense gliosis in the area of myelin loss although the axis-cylinders remained practically intact. The close resemblance to the lesions of multiple sclerosis has led these experimenters to believe that the same histological sequence must occur in this process also. Further studies along these lines will be awaited with interest.

TREATMENT OF PATIENTS SUFFERING FROM MULTIPLE SCLEROSIS

It is difficult to judge of the effect of any therapy in multiple sclerosis because of the frequent remissions that naturally occur in the course of the disease with or without treatment. Moreover, some cases are very benign and of long duration, whereas others are much more severe and acute in their course.

On the theory that the disease is of spirochaetal origin many attempts have been made to treat patients with silver preparations and with arsenicals (silver salvarsan). The results, however, were not encouraging. Better results are said to have been obtained by Otto Marburg through the use of an antimony preparation ("Fuadin") by intramuscular injection, a series of injections being repeated every three or four months.

The use of malarial therapy (as in general paresis), or of injections of typhoid vaccine, or the production of fever in some heating apparatus are said to have caused remissions in some cases, but one can-

not be sure that the remissions were due to these procedures, since remissions occur without therapy; moreover, such strenuous measures scarcely dare be applied except in patients who are fairly robust.

Those who assume the hypothesis of a metatuberculous process rely upon tonic measures and increase of the natural resistance of the body.

As will be seen from these comments, there has been but little if any progress made in the treatment of disseminated sclerosis in recent years. And in trying new methods of treatment, any one of which may doubtless be followed by a remission, I would warn strongly against the assumption that the remission is due to the therapy. We must hope that further study of etiology and pathogenesis may give us new clues for better therapeutic intervention. It is possible that the studies of abnormal lipase activities and their relation to the demyelinization process may represent a step in this direction.

Recently, Royle in Australia and F. S. Wetherell in Syracuse have resorted to the operation of bilateral cervico-dorsal sympathectomy as a treatment for multiple sclerosis, with the idea of improving the circulation and decreasing the irritation in the central nervous system. They report improvement in the condition of the patients thus treated, but more time must elapse before a safe judgment regarding the efficacy of this treatment can be formed.

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MORPHOLOGIC CHANGES IN THE BLOOD ASSOCIATED WITH EXPERIMENTALLY PRODUCED HEPATIC DAMAGE[1,2]

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Submitted for publication March 4, 1936

In 1933 the writers called attention to the macrocytic anemia which is occasionally found in association with disorders of the liver and pointed out that the blood picture closely resembles that of pernicious anemia (21). The etiology of the anemia was considered with reference to (*a*) the accidental coexistence of pernicious anemia and liver disease; (*b*) the possible influence of bilirubinemia or other chemical changes in the blood causing macrocytosis through physicochemical effects on the circulating erythrocytes; and (*c*) the relation of functional changes in the liver and of achlorhydria to the development of the anemia. It was suggested that the anemia might be the result of faulty storage or of failure to elaborate in the liver the hematopoietic principle (Castle), deficiency of which results in the development of macrocytic anemia.

The macrocytic anemia associated with disorder of the liver has received the attention of continental investigators from time to time for a number of years, but until 1933 only one reference to it had been made in the English literature. The numerous clinical reports which have recently appeared not only indicate the present interest in this anemia, but also bear witness to the relative frequency with which the syndrome occurs. We have reviewed the literature elsewhere (21, 20).

The study of a large number of cases of liver disease of varying grades of severity and duration (20) disclosed the fact that, unless hemorrhage had occurred, the anemia associated with hepatic disorder

[1] Aided by a grant from the Ella Sachs Plotz Foundation.

[2] Read at a meeting of the Johns Hopkins Medical Society, February 10, 1936.

[3] Stephen C. Clark Fellow.

was either normocytic in type, or macrocytic. Examination of the clinical records and of the organs at autopsy revealed that macrocytic anemia occurred only when the liver damage was of long duration and very widespread.

EXPERIMENTAL STUDIES

With the information derived from clinical and pathological studies it was obvious that the experimental production of the macrocytic anemia of liver disease would require a method for producing extensive liver damage of long duration. Carbon tetrachloride was chosen for this purpose, because Lamson and Wing (9) had already shown that cirrhosis can be induced by repeated administration of this drug and that the cirrhosis is strikingly similar to the Laennec cirrhosis observed in man. Furthermore, the extensive pathological studies of Gardner *et al.* (3), as well as those of Lamson and Wing (9), indicate that the damage caused by carbon tetrachloride is limited to the liver.

Materials and methods. Studies were made upon dogs, rabbits, and rats. The observations in rats may, however, be dismissed very briefly because of our failure to produce severe chronic liver damage in these animals. Deaths from cardiac puncture and from acute carbon tetrachloride intoxication prevented observations over a long period of time. As this manuscript was being prepared, a preliminary report by Higgins and Stasney (6) appeared in which they recorded the successful production of cirrhosis of the liver and macrocytic anemia in rats by the administration of carbon tetrachloride. In our experiments this drug was given by gavage, whereas Higgins and Stasney administered it by inhalation. The method of administration may perhaps explain the difference in our results.

Eleven mongrel dogs, 8 males and 3 females, were given carbon tetrachloride over periods ranging from 2 to more than 23 months. Three additional animals were observed for a shorter period. The carbon tetrachloride was administered by gavage in measured amounts at intervals of from 3 times weekly to once every one or 2 weeks. The average dosage per animal varied from 0.92 to 7.0 cc. per kilogram per week. The total amounts given varied from 150 to 3500 cc. The dose in each dog was altered from time to time in an effort to cause repeatedly the maximum sublethal damage.

The animals were kept in cages indoors during the winter months

and in an open yard during warmer weather. Most of them were immunized against distemper at the beginning of the experiment. The diet consisted of boiled beef lungs and white wheat bread. Cod-liver oil and whole cow's milk were given occasionally. Approximately 10 grams of a mixture of equal parts of calcium carbonate and calcium chloride were also administered daily.

The diet selected was particularly suitable for the purposes of our experiment. Minot (10) and others (8) have demonstrated the rôle which calcium plays in diminishing the acute toxic effects of carbon tetrachloride. Cutler (2), and Bollman and Mann (1) have shown that dogs maintained on a purely meat diet are more susceptible to the toxic effects of the drug than those receiving an ample supply of carbohydrates. In addition, the latter authors found that animals on a meat diet are more likely to develop complications such as ascites or hemorrhage. It is for these reasons that an abundance of calcium and of carbohydrates was included in the diet.

Similar experiments were carried out upon 11 rabbits, 8 males and 3 females, over periods ranging from 3½ weeks to 8 months. Twelve additional rabbits were observed for shorter periods. The rabbits, all adults weighing from 1850 to 3400 grams, were kept in individual cages and maintained upon a diet of whole wheat, oats, hay, and water. One teaspoonful of the calcium mixture given to the dogs was mixed daily with the wheat or oats. The carbon tetrachloride was given once or twice a week or even daily and the dosage per rabbit varied from 0.11 to 2.13 cc. per kilogram per week. As with the dogs, the dose was frequently altered in each instance in an effort to obtain the maximum liver damage and at the same time the maximum survival. The total amount of carbon tetrachloride given varied from 0.9 to 69.0 cc. At the beginning of the experiment the drug was administered by gavage; subsequently, in a few animals, it was delivered into the posterior pharynx by pipet.

Blood was withdrawn at weekly or semiweekly intervals. Three cubic centimeters were obtained by jugular puncture in the dogs and 1 to 2 cc. were taken from the marginal ear vein of the rabbits. The blood was collected in bottles containing 1.3 mgm. of dried ammonium oxalate and 0.7 mgm. of dried potassium oxalate per 1 cc. of blood,[4]

[4] No change occurs in the size of red corpuscles of dog or rabbit blood to which this anticoagulant has been added.

and was examined in the manner previously described by one of us (19). Erythrocyte determinations, hemoglobin, volume of packed red cells, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, and volume of packed white blood cells and platelets were determined regularly. On occasion, erythrocyte diameter measurements and leucocyte counts were made.

Blood studies and the weights of control animals subjected for periods of 9 to 11 months to exactly the same conditions as the experimental animals indicated that their diet was adequate and that the amount of blood withdrawn did not cause anemia. Normal blood values were determined on samples taken in the manner described and are based on 173 determinations in 54 normal dogs and 168 determinations in 61 normal rabbits (22).

Liver damage was estimated by icterus index determinations made each week, and from van den Bergh studies and bromsulphthalein tests, as well as by gross and microscopic examination of the livers at autopsy.

In a number of the dogs gastric analyses (histamine method) and total blood volume measurements (brilliant vital red) were carried out. In addition, total plasma solids, total proteins, and refractive index of the blood were determined in certain animals.

Autopsy was done in every instance except on two dogs (A53 and A95) which are still under observation. Microscopic sections of the liver and spleen and of the marrow of a rib, femur, vertebra, and the sternum were studied. In a number of animals lungs, kidneys, and pancreas were also examined microscopically. The livers were stained with hematoxylin and eosin, hematoxylin and Van Gieson's stain, and according to Laidlaw's modification of Rio-Hortega's lithium silver carbonate method for reticulin and collagen.

RESULTS

Clinical effects of carbon tetrachloride administration. Dogs. A217 and A218, each of which received 8 cc. per kilogram in a single dose, exhibited lassitude and anorexia for several days. In the other dogs, given smaller doses, symptoms were very rare even when the drug was administered three times weekly. The animals continued to be

normally active and ate well. Eventually, however, in spite of absence of anorexia and vomiting, most of the dogs gradually lost weight. In some the weight loss occurred early and was marked. In 4 the loss of weight was slight or moderate and in 4 others it was very great, being as much as 54 per cent in one animal. One young dog continued to

FIG. 1. Abdominal distension due to ascites. Dog A54, treated with carbon tetrachloride. Photograph one week before death.

gain weight and two fully developed dogs weighed more at the termination of the experiment than at its commencement. One of the latter, however, developed ascites.

Three and a half months after carbon tetrachloride was first given this animal (A54) began to gain weight rapidly. Five weeks later massive ascites was evident (fig. 1). In spite of abdominal para-

centeses with removal of as much as 900 cc. of amber-colored fluid each time, the accumulation of fluid increased. The superficial abdominal veins became dilated and tortuous, and the lower abdominal wall, genitalia and thighs became edematous. No other dog developed ascites.

Bollman and Mann (1) describe gastro-intestinal upsets, diarrhoea, and intestinal hemorrhage as occurring frequently in their series. Chronic and subacute duodenal ulcers developed in many of their animals. We noted no vomiting or diarrhoea except in the two surviving dogs (A53 and A95) and in one (A84) which survived a long time. In these animals, vomiting a half to two hours after administration of carbon tetrachloride was discovered. At no other times was vomiting observed and only in one animal (A84) was diarrhoea ever noted. In all instances the stools remained normal in color and consistence. Only in one dog (A58), which developed an acute duodenal ulcer, were we able to find evidence of ulceration or bleeding from the gastro-intestinal tract.

Icterus index was elevated in 5 of the 11 dogs. In 2 the increase was moderate and in 3 it was very marked and well sustained. The highest observed value (60) was found in A56 2 months after carbon tetrachloride administration was begun. It is quite probable that increases in icterus index were often missed, because blood specimens were usually taken not at the time of maximal acute liver destruction (48 hours after administration (9)), but several days following the administration of carbon tetrachloride.

Bromsulphthalein tests were carried out at intervals on 9 of the dogs. All except one (no determination was made on this animal during the period of most severe liver damage) showed some retention (table 3).

Rabbits. In general, we found, in confirmation of the observations of Gardner *et al.* (3), that rabbits are much more sensitive to carbon tetrachloride than are dogs. Although we were able to give repeated doses of the drug in some instances over periods as long as 8 months, only 11 rabbits survived administration of carbon tetrachloride for more than $3\frac{1}{2}$ weeks (table 4). Twelve rabbits died in from one to 15 days after doses totaling 0.1 to 2.2 cc. per kilogram. Listnessness and prostration were the only symptoms observed in the rabbits. Five which survived for several weeks lost weight. In none was ascites or intestinal hemorrhage noted.

Icterus index was moderately elevated in 2 of the rabbits, markedly increased (50) in one. As with the dogs, transient rises were probably missed. Bromsulphthalein tests were done on only 2 rabbits. Both showed retention (table 4).

In the dogs and in the rabbits we were impressed with the individual variation in susceptibility to the toxic effects of carbon tetrachloride. This was evident clinically in the rabbits, a single dose of 0.2 cc. being fatal in some instances, while, on the other hand, one rabbit received 69 cc. over a period of $27\frac{1}{2}$ weeks with daily doses of 1 cc. for long intervals. Variation in susceptibility was also observed in the dogs, but in these animals the rôle of regurgitation of carbon tetrachloride must be taken into consideration. As already stated, this occurred many times in 3 animals and may have taken place unnoticed in other dogs. This could not, however, have been a factor in the rabbits, since vomiting does not occur in these animals.

Effects on the blood. As a general rule, the initial blood response following administration of carbon tetrachloride was a more or less marked polycythemia. With continued administration of the drug the number of erythrocytes tended to fall to normal and subsequently moderate anemia developed. Frequently, because of fear of losing the animals, when marked changes in the blood took place, carbon tetrachloride was given less often and in smaller amounts. Ordinarily this was followed by restitution of the blood to normal, or when anemia persisted, this at least ceased to increase in degree. As the dosage was again increased another period of polycythemia frequently occurred. Eventually the animals tended to become anemic and to remain so. The anemia was at first normocytic in character, but in a few animals, as the anemia increased, distinct macrocytosis developed.

Polycythemia. In table 1 are shown the polycythemic changes in the blood of the dogs. At one time or another 9 of the 14 animals showed an abrupt and significant polycythemia. Seven showed a very definite increase following the initial doses of carbon tetrachloride; 5 of the 7 subsequently manifested a second or even a third polycythemic phase, which invariably occurred after the dosage had been suddenly increased. Two dogs which failed to show an initial polycythemia developed polycythemia later when the dosage was abruptly increased. It is probable that in certain instances we may have failed to demonstrate a transient polycythemia because blood examinations

TABLE 1

Polycythemia in dogs following administration of CCl_4

NUMBER	BLOOD EXAMINATION BEFORE AND DURING POLYCYTHEMIC PERIOD						DEGREE OF INCREASE IN HT. OR R.B.C.	REMARKS
	R.B.C.*	Hgb.	Ht.	C.V.	I.I.	Days after Rx		
							per cent	
A53	6.97	14.2	49.2	70	6			Polycythemia began after 5 doses of 2 cc.†
	7.86	18.2	55.7	71	6	24	13	
	6.74	14.4	43.0	64	15	45		Occurred again after increase in dosage from 0.8 to 1.7 cc.
	7.41	16.6	51.0	68	22	67	19	
	6.69	14.0	43.3	65	7	613		Recurred after another abrupt increase in dosage from 4.0 to 7.0 cc.
	7.96	16.8	52.1	65	7	638	20	
A54	5.90	12.3	39.2	67	6			Initial increase noted after 2 doses (0.7 cc.)
	7.03	14.1	48.0	68	6	3	23	
	6.57	14.5	45.4	69	12	120		Occurred again after increase in dosage from 1.2 to 2.1 cc.
	8.05	15.2	51.8	64	8	163	21	
A56	6.61	13.6	42.6	64	6			Polycythemia noted 3 days after administration of 2 doses (0.6 cc.). A subsequent rise occurred after increase in dosage. See fig. 2
	8.60	19.8	56.8	65	5	24	33	
A58	7.26	15.9	49.1	68	6			Polycythemia reached maximum 2 weeks after onset of Rx, after 3 doses (2.5 cc.)
	9.14	20.0	58.9	65	7	14	26	Occurred again after increasing the dosage
A84	5.38	11.8	35.1	65	7	414		No initial polycythemia, but marked change later after increase in dosage from 3.4 to 5.1 cc.
	6.96	15.0	46.1	67	7	432	31	
A95	6.10	12.6	41.6	68	10			Initial increase after 2 doses (4.8 cc.)
	7.65	14.9	49.0	64	7	5	24	
	6.82	14.1	44.0	65	7	172		Occurred after doubling the dosage (2.0 to 4.0 cc.)
	7.80	16.2	51.0	65	7	200	16	
	6.50	13.7	42.9	66	8	394		After increase in dosage (5.4 to 9.0 cc.)
	7.56	15.1	49.2	65	6	434	16	

TABLE 1—*Concluded*

NUMBER	BLOOD EXAMINATION BEFORE AND DURING POLYCYTHEMIC PERIOD						DEGREE OF INCREASE IN HT. OR R.B.C.	REMARKS
	R.B.C.*	Hgb.	Ht.	C.V.	I.I.	Days after Rx		
							per cent	
A96	6.91	13.8	42.6	62	7			No initial polycythemia. Pronounced change later after marked increase in dosage (0.3 to 1.4 cc.)
	7.52	15.3	50.5	66	7	188	19	
	6.84	15.1	44.0	64	7	275		Subsequent rise after increase in dosage (1.1 to 6.0 cc.)
	7.32	17.8	48.2	66	7	294	10	
A217	7.93	16.5	55.0	69	7			Began 2 days after a single dose of 8 cc.
	8.83	19.7	62.3	70	7	2	13	
A218	6.56	13.2	44.0	67	7			Began 2 days after a single dose of 8 cc.
	7.75	16.4	52.2	67	7	2	19	

* In all tables, R.B.C. refers to red cell count in millions per c.mm., Hgb. to hemoglobin in grams per 100 cc., Ht. to volume of packed red cells in cc. per 100 cc., C.V. to mean corpuscular volume in cubic microns, C.H. to mean corpuscular hemoglobin in micromicrograms, C.C. to mean corpuscular hemoglobin concentration in per cent, and I.I. to icterus index in units.

† All dosage of CCl_4 is given in cubic centimeters per kilogram per week.

No polycythemia was noted in dogs A72, A74, A86, A94, and A98, which are omitted from this table.

For normal values in dogs, see table 3.

were not made daily. In figure 2 an example of the extent and duration of the polycythemia may be seen.

The maximum increase in volume of packed red cells varied from 13 to 33 per cent. No significant change was noted in the size of the cells nor in their hemoglobin content during the polycythemic periods.

At no time did polycythemia occur except (1) following the initial administration of carbon tetrachloride or (2) after an abrupt increase in the dosage of the drug. We concluded, therefore, that this alteration in the blood was related to acute damage to the liver.

In an effort to determine the nature of the polycythemia, blood volume determinations were carried out in 3 dogs during the polycythemic phase and in 7 control animals. The total blood volume per kilogram of body weight in the 3 animals (A54, A56, and A58) was

103.2, 170.6, 133.0 cc., respectively, and that of the control dogs 47.0, 56.5, 67.3, 71.8, 75.3, 105.4, and 109.0 cc. Plasma volume per kilogram was correspondingly elevated, being 53.3, 79.2, and 57.9 cc., respectively, as compared with values of 27.4, 31.2, 31.6, 34.9, 36.3, 57.9, and 56.5 cc. in the normal dogs. The values during polycythemia averaged 135.6 cc. for total blood volume per kilogram and 63.5 cc. for plasma volume per kilogram, whereas the averages of the control values were 76.0 cc. and 39.4 cc. respectively. These data suggest, therefore, that an absolute increase in blood volume without hemoconcentration occurred.

Refractive index determinations, however, although not entirely conclusive, suggested that hemoconcentration may have played a rôle in the causation of the polycythemia. Studies made upon 4 dogs before and during periods of polycythemia showed increases in refractive index and in the estimated plasma proteins; in A53 the average refractive index was 1.3490 (6.00 grams) before and 1.3501 (6.55 grams) during polycythemia; in A72 it was 1.3491 (6.05 grams) as compared with 1.3499 (6.45 grams); in A84, 1.3501 (6.55 grams) as compared with 1.3512 (7.10 grams); and in A95, 1.3491 (6.05 grams) as compared with 1.3498 (6.40 grams). These values, however, are not entirely dependable since they represent the average of a series of determinations which tended to fluctuate considerably. Occasionally the refractive index before polycythemia rose to values found during polycythemia. More conclusive as suggesting hemoconcentration is the increase in total plasma solids from 0.0761 gram to 0.0825 gram per cubic centimeter of plasma, which occurred in A95 during the period of polycythemia.

In the rabbits similar polycythemia was observed (table 2). Of 18 animals given carbon tetrachloride, 8 showed a definite increase in the number of cells and in volume of packed red cells. The maximum observed increase varied from 16 to 40 per cent. In 7 the rise occurred shortly after the first few doses of the drug were given. One rabbit showing no such initial response subsequently developed polycythemia after the dosage of carbon tetrachloride was abruptly increased.

Anemia. Dogs. After the carbon tetrachloride had been administered many times a large proportion of the animals developed anemia (table 3). Only one of the 11 dogs failed to do so. It was this animal (A54) which had massive ascites necessitating abdominal paracenteses,

TABLE 2

Polycythemia in rabbits following administration of CCl_4

NUMBER	BLOOD EXAMINATION BEFORE AND DURING POLYCYTHEMIC PERIOD						DEGREE OF INCREASE IN HT. OR R.B.C.	REMARKS
	R.B.C.*	Hgb.	Ht.	C.V.	I.I.	Days after Rx		
							per cent	
A71	5.84	10.3	33.0	57	7			Increase noted 2 days after the initial dose of 0.9 cc. per kilogram
	6.06	12.5	38.8	64	9	4	18	
A80	6.38	12.7	39.9	63	5			Maximum increase 2 days after initial dose of 0.5 cc. per kilogram
	7.76	14.0	46.5	60	12	2	21	
A93	5.84	11.2	34.5	59	8			Pronounced polycythemia 2 days after first dose of 0.3 cc. per kilogram
	8.20	14.3	48.1	59	7	2	40	
A101	6.88	13.5	42.6	62	7			Following two initial doses of 0.1 cc. per kilogram
	7.55	18.0	52.2	68	5	3	22	
A118	5.65	12.4	39.5	67	7			Following initial dose of 0.1 cc. per kilogram
	6.77	13.7	43.7	65	7	4	20	
A120	5.96	13.1	37.2	62	7			No initial polycythemia. This occurred later after increase in dosage from 0.4 to 0.95 cc. per kilogram per week. See fig. 4
	6.78	14.3	42.6	63	7	130	15	
A145	5.92	12.7	39.5	66	7			Began a week after first 2 doses of 0.2 cc. per kilogram. Maximum 3 weeks later
	7.01	16.2	46.8	66	6	29	18	
A209	6.06	12.6	39.9	66	7			After 5 doses of 3.0 cc. per kilogram per week
	6.86	15.8	46.4	68	7	26	16	

For normal values for rabbits, see table 4.

No definite polycythemic phase was observed in the rabbits which are omitted from this table.

and it is possible that subsequent hemoconcentration may have masked a terminal anemia.

In most of the animals anemia developed after a relatively long

TABLE 3

Anemia in dogs with experimentally produced liver damage

NUMBER	BLOOD EXAMINATION BEFORE TREATMENT AND AT LOWEST SUBSEQUENT LEVEL								PERIOD OF TREATMENT	CCl_4 PER KGM. PER WEEK	TOTAL CCl_4	ANEMIA			EVIDENCE OF LIVER DAMAGE		
	R.B.C.	Hgb.	Ht.	C.V.	C.H.	C.C.	I.I.	Weeks after treatment				Onset after treatment	Duration	Type	Highest icterus index	Highest bromsulphthalein retention	Autopsy
									weeks	*cc.*	*cc.*	*weeks*	*weeks*			*per cent*	
A53	7.28	14.3	48.6	67	20	31	8										Still living
	5.60	12.0	39.0	69	21	31		27						Normocytic		20	
	4.95	11.8	34.1	69	23	34	7	74	100	2.50	3,500	26	21		22		
A54	5.90	12.3	39.2	67	21	31	5										
	5.80	10.8	37.0	64	19	30	12	23.5	25	2.10	459	No anemia			33		++++
A56	6.61	13.6	42.6	64	21	32	6										
	3.98	9.5	31.0	78	23	31	20	17						Macrocytic			++++
	0.79	1.3	6.8	86	16	19	4	22	22	0.92	257	13	9		60		
A58	7.26	15.9	49.1	68	22	32	6										
	5.56	13.2	40.4	73	24	33	10	19.5						Macrocytic			++++
	4.45	10.0	31.6	71	22	31	50	22.5	23.5	1.35	378	17.5	6		50	20	
A72	7.28	14.3	48.6	67	20	31	8							Normocytic			
	5.30	10.9	34.4	65	21	32		19	19	4.50	687	17	2		7		+++
A74	7.02	13.2	46.2	66	19	30	8							Normocytic			
	4.02	7.0	26.0	65	18	28	6	22	24	1.69	460	17	7		25	30	+++

A84	7.22	14.9	50.4	70	21	30	9									
	4.13	9.1	28.0	68	22	32	3	9					Normocytic			
	7.18	16.1	48.0	67	22	34	6	74	74	1.49	1,700	4	56		10	5	+++
A94	6.89	14.0	46.1	67	20	30	8							Normocytic			
	4.66	9.9	31.5	67	21	32	6	13	27	1.24	207	10	17		8	8	++
A95	6.10	12.6	41.6	68	20	30	10										Still living
	4.75	11.6	35.8	75	23	31	4	5						Normocytic			
	7.80	16.2	49.5	65	21	33	6	29	74	3.67	1,620	5	4		12	6	
A96	7.39	14.6	48.4	66	20	31	9										
	4.60	10.0	31.0	63	22	32	4	4									++
	5.76	12.9	40.2	70	22	32	4	7						Normocytic			
	6.32	14.0	41.2	65	22	34	7	48	50	2.20	1,195	4	3		10	35	
A98	6.35	12.7	42.4	66	19	31	11							Normocytic			
	5.49	10.8	35.4	65	21	31	3	7	9	1.36	150	3	6		14	35	+++

Normal values (22)

Mean...	7.02	14.6	47.3	67.6	21.2	31.4
One S.D.	0.66	1.4	4.7	3.6	1.4	1.6

period of administration, which varied from 10 to 29 weeks. Three developed anemia more rapidly (3 to 5 weeks). Although there were wide fluctuations, the anemia persisted until death in 6 of the 10 animals. In 4 the anemia disappeared after 3 to 56 weeks in spite of continued administration of carbon tetrachloride. In three of these 4 animals, as already stated, regurgitation of the drug was repeatedly observed. In the fourth animal (A96), the amount of liver injury observed on microscopic examination was surprisingly small in view of the large doses given and the duration of treatment. In this dog it seems very probable that regurgitation of carbon tetrachloride had passed unnoticed.

In all of the anemic dogs the erythrocyte count dropped below 5.50 million; in 7 of the 10 it fell below 4.75 million. In one animal (A56) the red cells decreased to 0.79 million.

The anemia was either normocytic or macrocytic. As anemia developed in the dogs, an increase in anisocytosis was noticeable, and one gained the impression from the examination of the blood smears that there were more large cells than small ones. This, however, was usually not great enough to cause a significant increase above the normal in mean corpuscular volume or diameter measurements. For example, although the mean corpuscular volume of dog A74 during the last month of life never rose above 67 c. μ., smears of the blood, as compared with those before treatment, showed more anisocytosis with a tendency to macrocytosis. Values as high as 71 c. μ. were not uncommon in several dogs (A53, A96) but this could not be definitely considered to represent macrocytosis (22). As the anemia tended to disappear following a reduction in the amount of carbon tetrachloride given and a decrease in frequency of administration, this slight increase in corpuscular volume disappeared as well.

These changes may have represented the beginning of macrocytic anemia, but in most instances the dogs died of liver damage before further changes took place in the blood. In two instances, however, significant macrocytosis was present over a long period of time (Dogs A56 and A58, table 3, figs. 2 and 3).

The morphologic changes in the blood of A56 deserve special description. When the erythrocyte count had decreased to 5.00 million cells slight anisocytosis and poikilocytosis were evident in the

smears. Two weeks later when the red cells numbered 4.50 million and the mean corpuscular volume was definitely elevated (75 c. μ) there was a rather general macrocytosis, with slight anisocytosis and occasional polychromatophilia. As the red cell count dropped, more

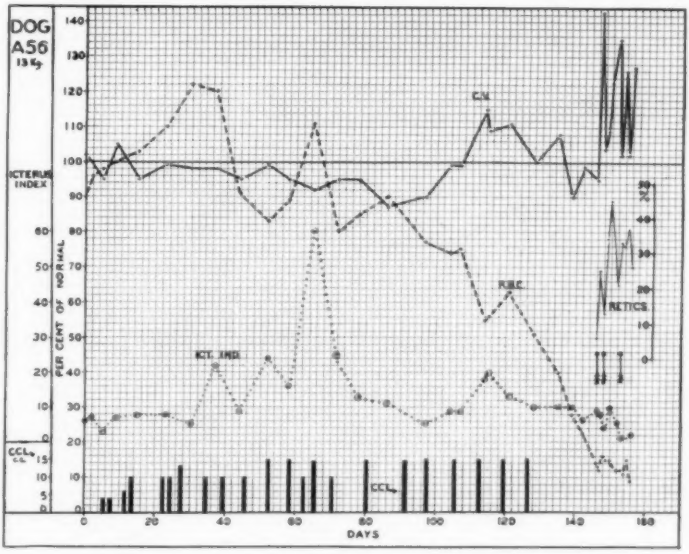

FIG. 2. Red cell count (R.B.C.), mean corpuscular volume (C. V.), reticulocytes, and icterus index of a dog (A56) which developed severe macrocytic anemia following liver damage induced by the administration of carbon tetrachloride. Note the early phases of polycythemia. The arrows indicate times of injection of liver extract (Lilly, 343) 10 cc.

In this and the following charts values for red cell count and mean corpuscular volume are represented in proportion to the normal for the animal. Red cell counts are represented by an interrupted line, mean corpuscular volume by a continuous line, and icterus index by a dotted line.

and more macrocytes, more microcytes, moderate polychromatophilia, and even nucleated red cells appeared. Poikilocytosis was never prominent. Achromia was variable in degree but the larger cells were usually well filled with staining material. Occasional cells containing Isaacs' granules appeared as the anemia increased. Ten days before

death when the red cell count was 1.09 million, the differential leucocyte count was essentially normal, there being 2 per cent juvenile neutrophils, 68 per cent segmented neutrophils, 1 per cent eosinophils, 2 per cent basophils, and 28 per cent adult lymphocytes. There was leucopenia (1750 cells per cubic millimeter), however, and 16 nucleated red cells were present per 100 white cells. The nucleated erythrocytes were chiefly normoblasts, although an occasional one was exceptionally large. Typical megaloblasts were not observed. Platelets were not enumerated but seemed to be scarce in the smear.

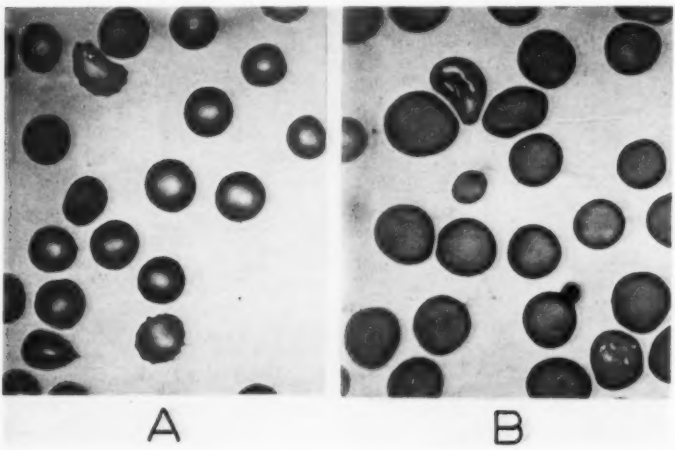

FIG. 3. Photomicrograph of the blood of dog A56. (Magnification ×1035, Wright's stain.) A, before treatment was instituted; B, 4 days before death.

In this dog marked reticulosis was observed shortly before death, following administration of intramuscular liver extract (N.N.R. No. 343) in two doses of 10 cc. each (fig. 2). The maximum value for reticulocytes (45 per cent) was found on the fourth day following injection of the liver extract. After this, the values fluctuated considerably. Liver therapy was attempted in this animal only and it is consequently impossible to be certain that the reticulocytosis was not coincidental.

Leucocyte counts were not done on the other dogs, but judging from

the volume of packed white cells and platelets it is probable that in a number of them leucopenia occurred. The volume of packed leucocytes and platelets fell to 0.3 cc. or less in A53, A58, A74, and A84 during periods of slight or moderate anemia. Normally the volume of packed white cells and platelets varies from 0.7 to 1.5 cc. per 100 cc. of blood.

Rabbits (table 4). Essentially the same changes were observed in the rabbits as were noted in the dogs with the exception that anemia did not occur so regularly (most probably because survival was not so uniformly prolonged) and macrocytosis developed somewhat more frequently.

Anemia was observed in 7 of 11 animals. In several others there was a slight reduction in the number of erythrocytes. The onset varied from one to 11 weeks after administration of carbon tetrachloride was begun. The anemia persisted until death in 4, while in 2 animals it disappeared after a short interval but returned later to persist until the end. The erythrocyte count fell below 5.00 million in 6 of the 7 anemic rabbits, below 4.20 million in 5. The anemia was normocytic in 4 instances, macrocytic in 3.

In rabbit A143 the amounts of carbon tetrachloride were decreased as the anemia appeared. This was followed by a rise in the erythrocyte count and the animal died before anemia again developed. In two other animals in which normocytic anemia occurred (A80, A145) the anemia was only slight in degree. Only in one instance (A93) was the normocytic anemia severe. It is noteworthy that in all three instances in which macrocytic anemia developed (rabbits A71, A120, A146) the anemia was well marked. The steady increase in mean corpuscular volume as anemia progressed is shown in figure 4.

Examination of the blood smears corroborated the macrocytosis as determined by mean corpuscular volume studies. In fact, a few macrocytes could be seen in the smears before the mean volume of the cells was found to be increased. Thus, in rabbit A146 on the 169th day definite macrocytes as well as slight polychromatophilia were observed. There was little poikilocytosis. Two weeks later these changes were more marked, and after another ten days there were many macrocytes and a moderate number of microcytes. All the cells were well filled with hemoglobin and some of the macrocytes were

TABLE 4

Anemia in rabbits with experimentally produced liver damage

NUMBER	BLOOD EXAMINATION BEFORE TREATMENT AND AT LOWEST SUBSEQUENT LEVEL								PERIOD OF TREATMENT	CCl_4 PER KGM. PER WEEK	TOTAL CCl_4	ANEMIA			EVIDENCE OF LIVER DAMAGE		
	R.B.C.	Hgb.	Ht.	C.V.	C.H.	C.C.	I.I.	Weeks after treatment				Onset after treatment	Duration	Type	Highest icterus index	Highest bromsulphthalein retention	Autopsy
									weeks	*cc.*	*cc.*	*weeks*	*weeks*			*per cent*	
A71	5.81	10.3	33.0	57	17	31	7										
	3.17	7.2	21.5	68	23	33	15	4						Macrocytic			
	3.53	7.9	26.0	74	22	30	13	6	6.5	0.80	10.0	2	4		50		+++
A79	6.96	14.0	43.6	63	20	32	8										
	5.86	11.2	38.2	65	19	30	9	4	4.0	0.45	5.5	No anemia			21		+
A80	6.38	12.7	39.9	63	20	32	5							Normocytic			
	5.37	11.0	34.0	63	20	32	10	2.5	3.5	0.80	4.4	1.5	2		15		++
A93	5.84	11.2	34.5	59	19	32	8							Normocytic			
	3.33	6.0	20.1	61	18	30	8	4.5	4.5	0.11	0.9	2	2.5		8		+†
A120	5.56	11.0	35.4	64	20	31	6					3 (1)*	1	Macrocytic			
	4.05	10.6	30.0	74	26	35	—	32.5	32.5	0.80	54.4	25 (2)*	7.5		8	20	+++
A143	5.60	12.3	35.9	64	22	34	7							Normocytic			
	4.16	10.4	28.0	67	28	37	—	4	8	0.42	11.5	3	2		8		++
A145	5.92	12.7	39.5	66	21	32	7							Normocytic			
	5.06	11.2	34.5	64	21	34	7	7	8.5	0.28	9.0	7	1.5		8		++++

A146	6.28	13.3	40.4	64	21	32	7					11 (1)*	1				
	5.09	10.7	34.0	67	21	31	7	22						Macrocytic			
	3.81	10.0	30.9	80	26	33	7	26	27.5	0.82	69.0	17 (2)*	10.5		8	12	++++
A200	6.35	14.1	40.5	64	22	34	6										
	5.60	12.1	36.5	65	22	33	7	3	4.0	0.75	9.0	No anemia			7		++
A202	5.87	12.5	36.6	63	22	34	7										
	5.16	12.0	36.0	70	23	34	7	4.5	5.0	1.00	15.0	No anemia			7.5		+
A209	5.86	12.5	38.1	65	22	33											
	5.50	12.2	37.5	68	22	33		5	8.0	2.13	23.0	No anemia			7.5		No specimen
Normal values (22)																	
Mean...	6.29	13.0	39.8	63.7	21.0	33.2											
One S.D.	0.60	1.5	4.2	3.7	1.6	1.7											

* (1) and (2) denote the first and second periods of anemia.

† Coccidioidal cysts present.

polychromatophilic. Moderate poikilocytosis was present and bizarre cocked-hat and tailed forms were seen. Nucleated red corpuscles were rare.

The degree and character of the anisocytosis and macrocytosis found in 2 of the rabbits in which macrocytic anemia developed are shown in figure 5.

No significant changes were observed in differential leucocyte counts.

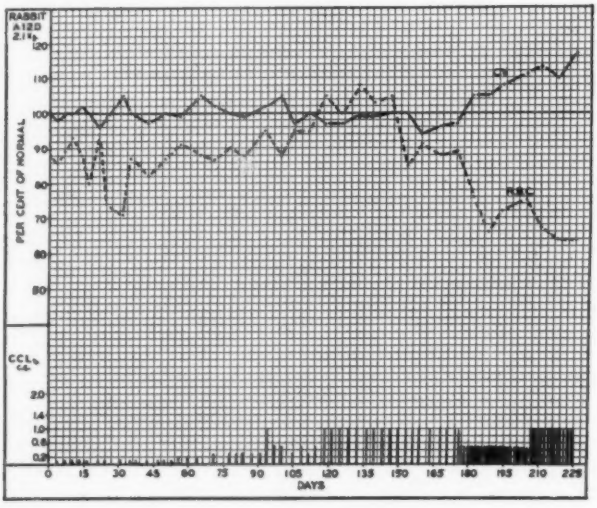

FIG. 4. Rabbit A120. As anemia progressed, there was a steady increase in the mean corpuscular volume.

Gastric analysis was done on 4 of the dogs. In 3 of the 4 (A53, A54, A56) there was no fasting free HCl, but free acid appeared after the injection of histamine. In the fourth dog (A58) there was a moderate amount of free HCl in the fasting specimen. No significance can be attached to the fasting achlorhydria, however, since 4 of 6 control dogs showed no free acid in the fasting specimen.

Autopsy findings. The animals showed various degrees of weight loss. In those with moderately severe anemia general pallor of the tissues was evident. Death was probably due to extreme anemia in one dog (A56). In another (A58) an acute perforated duodenal ulcer

was found. The abdomen of this animal was filled with bloody fluid. In one dog (A54) there was found a marked accumulation of ascitic fluid with tortuosity and dilatation of the superficial abdominal veins. There was no thrombosis of the portal or splenic vein in this dog, or in any of the other animals, nor was there any evidence of obstruction of the common bile duct. The lungs were normal in all but one of the dogs. In this animal (A84) terminal pneumonia was found. In

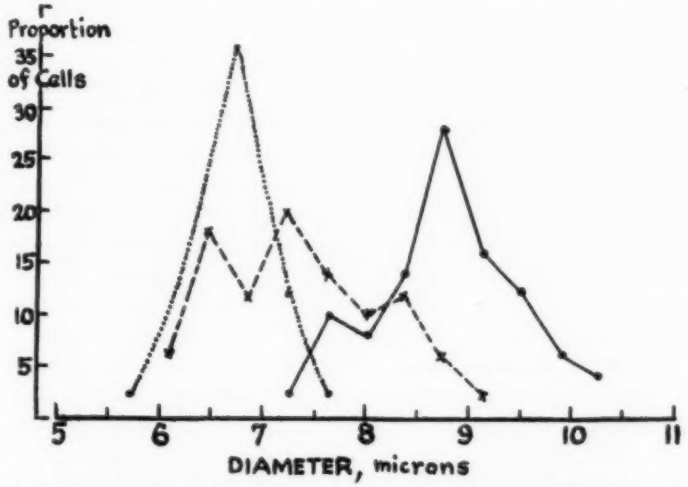

FIG. 5. Distribution of red cell diameters in the blood of two rabbits with macrocytic anemia, compared with the corpuscles of a normal rabbit.

Dotted line. Control rabbit (A115. R.B.C. 6.20, M.C.V. 64 c.μ., mean diameter 6.64μ.

Interrupted line. Rabbit A120 (Fig. 4), R.B.C. 4.05, M.C.V. 74 c.μ., mean diameter 7.38 c.μ.

Continuous line. Rabbit A146 (Fig. 9), R.B.C. 3.81, M.C.V. 80 c.μ., mean diameter 8.80 c.μ.

rabbits A78, 80, 120, 146, 202, and 204 the lungs showed terminal pneumonia on gross examination. Microscopic sections on two of these (A78, 80) confirmed this diagnosis. Some hemorrhage was noted in the lungs of A79, 81, 82, 89, 90, 92, 143, and 145. In the remaining animals no cause of death was found and it was assumed that they had died of hepatic insufficiency.

In addition to sections of lungs, liver, spleen, and bone marrow, the

pancreas, lymph nodes, and kidney of one dog (A56) were examined microscopically. The pancreas of one and the kidneys of 9 other rabbits were likewise studied histologically. No lesions were found in the pancreas or lymph nodes. The kidneys were essentially normal. These observations agree with the extensive studies of Gardner *et al.* (3), who concluded that the only significant lesions caused by carbon tetrachloride are found in the liver.

The livers of the animals which died shortly after one or a few doses of carbon tetrachloride showed the findings which Gardner *et al.* (3) have already described. Grossly, the livers were of normal consistence and rather pale. Red liver tissue could be seen in minute masses about the portal radicles while thin yellow bands were so distributed as to give a trabeculated appearance. Microscopically the lesion was found to be a central necrosis, but in many instances this was so extensive that only about the portal radicles could a few normal liver cells be recognized. In the necrotic areas, accumulations of red cells, free pigment, fragmented liver cells filled with granular material, or fat droplets could be seen. The nuclei showed various degrees of degeneration.

The livers of the animals which had received repeated doses of carbon tetrachloride presented a somewhat different picture and some of these may be described in detail.

Dog A54 (tables 1 and 3 and fig. 1, ascites). The liver was small and the surface was studded with a mass of nodules; it was light brown in color, firm, and gritty on section. The cut surface revealed small nodules outlined by rather wide bands pale in color. Microscopically, most extensive destruction of liver tissue with complete effacement of the liver architecture was seen. No more than 5 per cent of the liver cells remained. Surrounding the small masses of liver tissue were broad areas composed almost entirely of capillaries filled with decolorized red cells. Occasional old degenerated liver cells were seen. Iron pigment was scattered about diffusely, free and in the Kupffer cells. Some fibroblasts were seen but there was little scarring. Van Gieson's and Laidlaw's stains showed surprisingly little reticulin and collagen, only a little being present in the collapsed areas. In view of the ascites as well as the gross appearance and consistence of the liver, the amount of scarring was surprisingly small.

Dog A56 (tables 1 and 3, figs. 2 and 3, severe macrocytic anemia). The gross appearance was characteristic of atrophic cirrhosis. The liver was small, pale in color, firm to palpation, gritty on section, and the surface was covered with nodules of varying size (fig. 6). Microscopically, there was no semblance of the normal architecture. There was great collapse of liver tissue and very little normal tissue remained (5 to 10 per cent). Most of the cells stained poorly; their cytoplasm was vacuolated and granular while the nuclei showed varying degrees of degeneration. The liver cells were grouped together in small and

FIG. 6. Photograph of liver of Dog A56, showing advanced atrophic nodular cirrhosis following the administration of carbon tetrachloride.

large nodules, many of which had no apparent connection with either blood vessels or bile ducts. The nodules were separated from one another by bands of connective tissue. Very striking was the regeneration of bile ducts. Hemorrhage was slight and there was little round-cell infiltration. In places there was marked fatty degeneration. Van Gieson's stains showed a fine connective-tissue proliferation throughout the scars and Laidlaw's stain demonstrated moderately heavy deposits of reticulin and collagen surrounding the nodules (fig. 7).

Dog A58 (tables 1 and 3, moderate macrocytic anemia). The liver was small (247 grams), firm, and nodular, but the nodules were not so prominent as in the liver of A56. Microscopically (fig. 8), there was a pronounced cirrhosis. The normal architecture was utterly destroyed and nodules of liver cells were demarcated by broad bands of connective tissue in a pattern typical of Laennec's cirrhosis. Many nodules appeared devoid of connection with blood vessels or bile ducts. In the scarred areas there were isolated necrotic liver cells and some

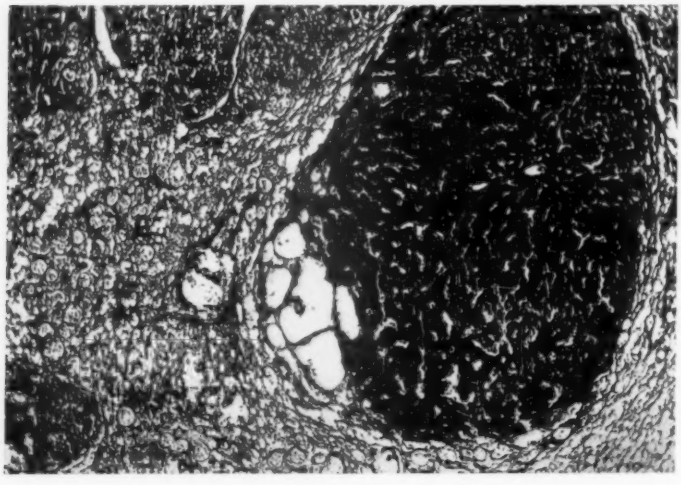

FIG. 7. Photomicrograph of liver of Dog A56. Laidlaw's connective tissue stain. Showing deposits of reticulin and collagen about a nodule of liver tissue. ×69.

hemorrhage as well as hemosiderosis, free and in macrophages. Some of the Kupffer cells were loaded with red blood cells. There was pronounced regeneration of bile ducts.

Rabbit A71 (tables 2 and 4, moderately severe macrocytic anemia). The liver weighed 74.2 grams, was pale yellow in color, and showed no nodules. Microscopically, there was moderate destruction of liver tissue and definite scarring. Bands of connective tissue tended to separate the liver cells in nodules, thus causing considerable distortion

of the normal architecture. There was almost no hemorrhage or hemosiderosis and only slight round-cell infiltration.

Rabbit A120 (tables 2 and 4, figs. 4 and 5, moderate macrocytic anemia). The liver was pale, quite firm, weighed 69 grams, possessed a distinct finely nodular surface, and was gritty on section. Microscopically there was moderately widespread necrosis of liver cells, the cytoplasm of the cells staining poorly with vacuolization and irregularity of outline, and the nuclei in various stages of disintegration.

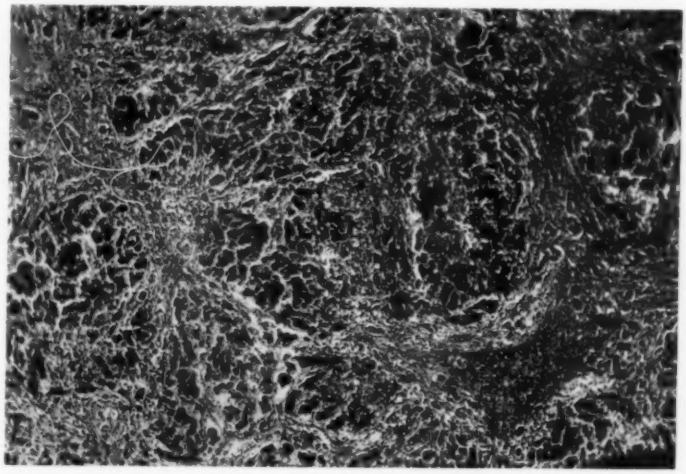

FIG. 8. Photomicrograph of liver of Dog A58. The similarity of the architectural pattern to that of Laennec's cirrhosis is apparent. H and E. ×69.

Acute destruction appeared to be superimposed upon chronic liver damage. There was some hemorrhage, slight round-cell infiltration, moderate regeneration of bile ducts. Laidlaw's stain showed bands of reticulin and collagen tending to surround and demarcate the masses of liver cells with light but distinct scarring.

Rabbit A146 (table 4, fig. 5, moderately severe macrocytic anemia). The liver was small (33.1 grams), deep red in color, and presented a slightly irregular surface. The sections (fig. 9) showed most extensive chronic damage. There were heavy bands of scar tissue which tended

to separate the nodules of liver cells. A considerable amount of liver tissue was lost and that remaining showed vacuolization, fatty changes, and degenerating nuclei. Some of the nodules appeared to have no connection with bile ducts or blood vessels. In the scarred areas a few necrotic liver cells, slight hemorrhage, very slight hemosiderosis, and some round-cell infiltration were present.

Changes of a similar character were observed in the livers of the other animals which had received repeated doses of carbon tetra-

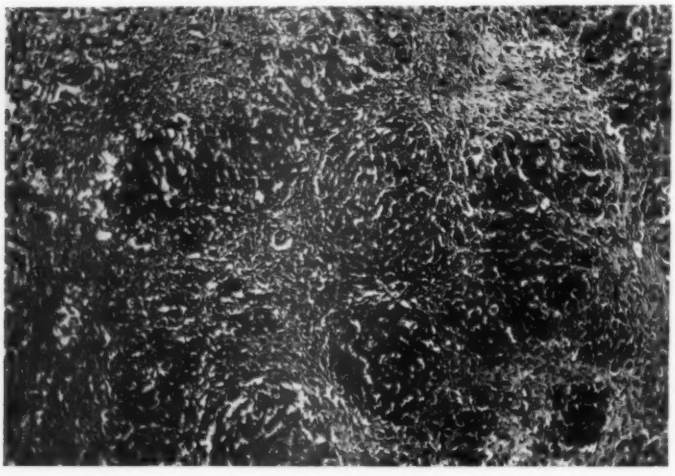

FIG. 9. Photomicrograph of liver of Rabbit A146. Heavy bands of scar formation surround small nodules of liver cells. H and E. ×69.

chloride, but the amount of damage varied considerably. An attempt has been made to estimate the degree of liver damage in each of the animals (tables 3 and 4). For this purpose the amount of scarring and of disorganization was accorded particular significance because it was considered important to distinguish recent injury by carbon tetrachloride from the permanent damage caused by previous doses.

It may be pointed out that in most of the instances in which very extensive liver damage of a chronic character was found, macrocytic anemia had been encountered. Thus, of the 3 dogs with the most

extensive cirrhosis, 2 (A56, A58) developed macrocytic anemia. The third (A54) was the animal which had ascites. Although the loss of liver tissue in this animal was very great, the amount of scarring was negligible in comparison with that observed in the livers of A56 and A58. The latter dogs presented the picture of the most advanced cirrhosis which was observed in the series. In the remainder of the dogs the liver damage was less extensive and usually of shorter duration, and in these animals normocytic anemia was observed.

In the rabbits the most extensive liver damage was found in A145 and A146. The latter showed well marked macrocytic anemia. The former animal showed only slight normocytic anemia, but it should be noted that it survived treatment with carbon tetrachloride for only a short period of time. The extent of liver damage in rabbits A71 and A120 was only less great than in A146 and in both macrocytic anemia developed. In the remainder of the rabbits there was less liver destruction, and either mild normocytic anemia or no anemia at all occurred. In the one rabbit (A93) in which there was slight liver damage and yet severe normocytic anemia, coccidioidal cysts were found in the liver.

The amount of chronic liver damage was not closely related to the amount of carbon tetrachloride which the animals had received, illustrating the enormous variation in susceptibility of the animals. For example, there appeared to be more chronic hepatic injury in A98, which had received only 150 cc. of carbon tetrachloride over a period of 9 weeks, than in A96 which had received 1195 cc. over a period of 50 weeks. As already stated, the discrepancy between the amount of carbon tetrachloride given the dogs and the degree of liver damage is probably in part accounted for by regurgitation of the drug.

The *spleens* were not remarkable on gross examination and microscopically they were normal except for a varying degree of hemosiderosis. In many instances this was of extraordinary extent, particularly in A58, A72, A74, A94, A96, A101, and A217. Extramedullary foci of blood formation (20) were not made out.

There was distinct hyperplasia of the *bone marrow* of rabbits A71, A120, and A146. These were the animals in which macrocytic anemia had been found. The vertebral marrow and that of the sternum and ribs was crowded with cells. The marrow of the femur

showed active hematopoiesis which contrasted with the fatty, inactive marrow (fig. 10) of the rabbits with normocytic anemia (A93, A143) as well as of normal rabbits and those treated for short periods.

The sternal marrow of rabbit A115 (control) was crowded with cells, most of which were nucleated red corpuscles possessing a pyknotic nucleus and a small rim of cytoplasm (normoblasts and microblasts). Larger nucleated red corpuscles were rare. A moderate number of myeloid leucocytes and megalokaryocytes were also present. The

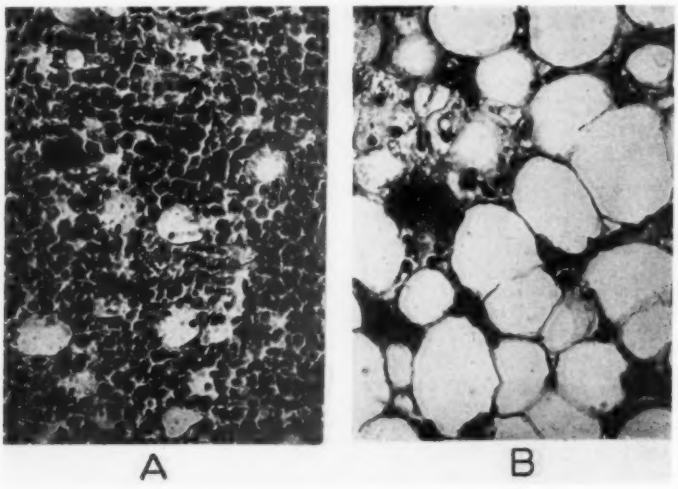

FIG. 10. Sections of femur marrow (A) of rabbit A120 (macrocytic anemia) compared with that (B) of a control rabbit (H. and E. ×266).

appearance of the sternal marrow of rabbits A71, A120, and A146 differed chiefly in that there were many larger nucleated red corpuscles with vesicular nuclei and a rather wide rim of cytoplasm (macroblasts). Rare cells showed nucleoli or mitosis. Comparison of the vertebral and femoral marrow of these animals revealed similar differences in the size and staining characteristics of the nucleated red corpuscles.

The vertebral, rib, and sternal marrow of all the dogs was red. That of the femur of A56 and A58 (macrocytic anemias) was deep red in

appearance, that of A72 and A74 (normocytic anemias) pale, and that of the remainder moderately red, but less deep in color than that of A56 and A58. Microscopic sections of these marrows were not entirely satisfactory but tended to show approximately the same degree of blood formation in the vertebrae, ribs and sternum of all the dogs. Smears of femoral bone marrow, however, revealed distinct differences between the cellular composition of the marrow of A56 (macrocytic anemia) and that of A74 (normocytic anemia) (fig. 11). That of the

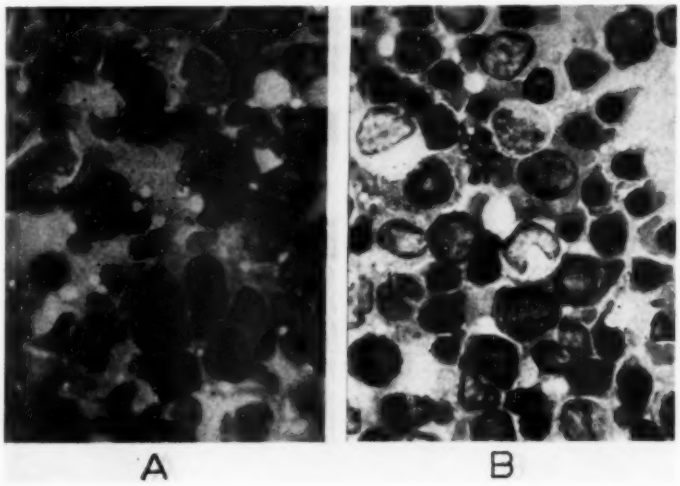

FIG. 11. Smears of femoral bone marrow (Wright's stain, ×724.) A, dog A74. normocytic anemia; B, dog A56, macrocytic anemia. Note the great number of erythroblasts in the latter as compared with the former.

former was very hyperplastic and contained numerous normoblasts with pyknotic nuclei as well as a number of macroblasts with nuclear chromatin of only moderate staining intensity and basophilic cytoplasm. There were, in addition, numerous non-granular leucocytes (myeloblasts) and a moderate number of myelocytes as well as occasional giant cells. Smears of the bone marrow of A74, on the other hand, showed few nucleated red corpuscles in comparison with the number of leucocytes, and those found were normoblastic in type.

DISCUSSION

The experiments described have amply confirmed the work of previous investigators (1, 3, 8, 9, 11, and 14) in regard to the toxicity of carbon tetrachloride for the liver. Following the administration of the drug, widespread central necrosis occurs. After repeated doses have been given over a long period of time, chronic changes occur in the liver and in many instances an anatomic picture practically indistinguishable from Laennec's cirrhosis develops.

Other than the changes in the blood, we have, like Gardner *et al.* (3) and Lamson and Wing (9), found the destructive effects of carbon tetrachloride to be limited to the liver.

The polycythemia which was observed in our animals was regularly associated with the administration of large doses of carbon tetrachloride and, therefore, presumably was related to acute, extensive destruction of the liver. Similar changes in the blood have been observed by Pisarski (13) in rabbits and in dogs poisoned with phosphorus, and recently Heath (5), using this substance as well as chloroform to induce acute liver destruction, observed polycythemia in rabbits. Polycythemia has also been observed clinically under similar circumstances (17, 15). Cases of cirrhosis with polycythemia, however, such as those described by Mosse (12) and more recently by Uhlhorn (18), probably do not fall into this category. Judging by the clinical descriptions and morphologic studies of the blood, their cases were instances of polycythemia vera with cirrhosis.

Taussig (17) thought that the polycythemia he observed in phosphorus poisoning was due to concentration of the blood through loss of fluids caused by vomiting. Pisarski (13), on the other hand, observed polychromatophilia and normoblasts in the circulating blood following acute phosphorus poisoning and concluded that the polycythemia was the result of irritation of the bone marrow by the drug. Heath (5), however, found no increase of reticulocytes or other evidence of increased blood formation in his animals and, as the result of serum protein studies, inclined to the opinion that hemoconcentration is the cause of the polycythemia.

In experiments concerned with acute liver damage caused by the administration of large doses of arsphenamine, Soffer (16) found no increase in the total proteins of the blood plasma in association with

the polycythemia which regularly occurred. Electrolyte changes, however, were such as would be associated with dehydration. In his dogs, moreover, there was marked diuresis and proteinuria and the latter was of such degree that it could account for the failure of the blood proteins to rise. He concluded, therefore, that dehydration is the cause of the polycythemia.

Our own observations are insufficient to permit conclusions to be drawn. The studies of blood volume suggest that an increase of total blood volume occurs without a decrease in plasma volume, but the studies of refractive index and plasma proteins favor the opinion that hemoconcentration occurred. It seems not unlikely to us that there is more than one cause for the polycythemia. A possibility which does not seem to have been considered so far is that red corpuscles stored in the liver (7) may be delivered into the circulation during the acute destructive changes which take place following the administration of hepatic poisons.

The anemia which developed in our experimental animals resembles in a rather striking manner the blood changes which have been observed clinically in instances of disorder of the liver (21, 20). It developed only following long continued and repeated damage to the liver, and was usually of moderate degree. While one gained the impression from examination of stained preparations and from slight increases in mean corpuscular volume that slight macrocytosis might be present in many instances, outspoken macrocytic anemia developed in only a small proportion of the animals. In these instances the macrocytosis was, in general, directly proportional to the severity of the anemia. As in the clinical series, macrocytic anemia tended to occur in those instances in which the liver damage was most extensive and of longest duration.

Three possibilities suggest themselves in regard to the cause of the anemia: (*a*) that it was the result of the direct influence of carbon tetrachloride on the circulating red corpuscles or on the bone marrow; (*b*) that it was secondary to liver damage; (*c*) that it was the result of some less apparent cause.

The possibility that the drug directly influenced the erythrocytes may be at once dismissed. The anemia was not hemolytic in character and, unlike the anemia which is associated with the use of hemolytic

agents, was not related to the dose of the drug. It may be pointed out, however, that Robbins (14) found carbon tetrachloride in higher concentration in the bone marrow of dogs treated with this drug than in any other organs examined. Nevertheless, direct action on the bone marrow seems unlikely because no bone marrow changes were noted in animals dying of acute carbon tetrachloride intoxication; indeed, no bone marrow changes were noted except in those animals which had developed *macrocytic* anemia. Secondly, it is unusual to find macrocytosis in anemia caused by drugs which affect the bone marrow, the picture ordinarily being that of an aplastic anemia. And finally, when bone marrow changes were noted they were hyperplastic rather than aplastic in type. This evidence is indeed indirect and not conclusive, but it does suggest that the anemia was not the result of the direct action of carbon tetrachloride on the erythrocytes or on the bone marrow.

In regard to the third possibility it can be stated that nothing was observed which suggested itself as a likely cause of the anemia. The gastro-intestinal upsets, diarrhoea, and intestinal hemorrhages which Bollman and Mann (1) describe were, with two exceptions, not encountered in our animals. Although regurgitation following administration of carbon tetrachloride occurred in several of the dogs, during the time when this was observed neither weight loss nor anemia developed. It is true that weight loss was common in our animals and frequently it was severe. There was no reason, however, to suspect that the anemia was due to malnutrition. Anemia did not develop in control animals on the same diet. Furthermore, a number of animals failed to show anemia even after they had lost a great deal of weight. Dogs A94 and A95 developed anemia of comparable degree although the former lost more weight than any other animal in the series, whereas the latter gained weight steadily. Rabbits A71 and A120, both of which developed macrocytic anemia, weighed more at death than at the onset of the experiment.

We are inclined to favor the second possibility, namely, that the anemia was indirectly the result of liver damage. The outstanding effect of carbon tetrachloride intoxication is damage to the liver. Moreover, as already stated, anemia developed only following prolonged treatment with carbon tetrachloride. There was a definite relationship between the severity and duration of the chronic liver

damage and the incidence of macrocytic anemia. Finally, the blood picture observed resembles very strikingly that of patients suffering from liver disease (20).

Since the antianemic principle of Castle is stored in greatest concentration in the liver, it is a reasonable assumption that the macrocytic anemia which occurs in association with severe and long-standing liver damage may be the result of faulty storage or of failure to complete the formation of this principle. This assumption is, at present, difficult to prove. The demonstration by Goldhamer *et al.* (4) that active antianemic principle was lacking in the liver of a patient who died of extensive cirrhosis with macrocytic anemia, supports the hypothesis. An attempt is being made at present to test the influence of liver extract on the macrocytic anemia associated with experimentally produced liver damage, and to determine the content of antianemic principle in the livers of animals with and without macrocytic anemia.

SUMMARY AND CONCLUSIONS

(1) The blood changes in dogs and rabbits in which acute and chronic hepatic damage was produced by the administration of carbon tetrachloride are described.

(2) Polycythemia developed following the initial doses of carbon tetrachloride or after the dosage was abruptly and substantially increased. The cause of this polycythemia is discussed.

(3) After injury to the liver was caused repeatedly and a chronic condition closely resembling cirrhosis was produced, anemia developed. This was usually normocytic in type, but in instances in which the liver damage was very severe and of long duration, macrocytic anemia occurred. In such instances the bone marrow was hyperplastic and macroblastic in type.

(4) The cause of the anemia is discussed. It is suggested that it may be the indirect result of liver damage and that the macrocytic anemia developed as the consequence of a fault in the internal metabolism of antianemic principle.

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AN UNUSUAL CASE OF DINITROPHENOL POISONING

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The following case report offers an excellent opportunity for studying the effects of small doses of dinitrophenol taken over a long period of time. Most of the cases of dinitrophenol poisoning reported in the literature have occurred in patients who manifested an idiosyncrasy to small doses of the drug, or in some who had taken massive overdoses. This patient took the drug in small doses during a period of about a year and a half without developing any alarming symptoms. But at the end of this time she developed marked symptoms of toxemia in spite of the fact that she had constantly limited herself to a small dose of the drug at weekly intervals. She also exhibited other noteworthy features among which were included a very high basal metabolic rate, absence of typical toxic skin manifestations, and prompt subsidence of the symptoms following withdrawal of the drug.

A 26-year-old graduate nurse, was admitted to the Johns Hopkins Hospital on Sept. 12, 1935 (unit Hist. No. 44260). The features of interest in her past history were that she had always been slightly over-weight and that she had been occupied with a very difficult nursing assignment for several months prior to the onset of the series of events recorded below.

During the month of November 1933, the patient consulted a physician because of "feeling sluggish" and "lacking energy." She was told that she was anemic and was given a prescription for capsules. These, she understood, contained an innocuous iron tonic. She was directed to take one or two of the capsules a week depending on their efficacy in dissipating the tired feeling of which she complained. During the next seven months she took two capsules a week and during the subsequent fourteen months took them at irregular intervals, skipping a week now and then when she was not conscious of the oppressive feeling of fatigue.

A definite subjective improvement resulted, which reached its peak during the fall of 1934. There was less obvious benefit during the spring of 1935. Coincidently with the decline in her subjective response, the patient began to have a series of staphylococcic infections—several boils, then an infected finger and then

several consecutively occurring hordeoli. Staphylococcic toxoid was administered to alleviate this condition and eventual improvement resulted.

During the spring of 1935, she developed a growing tendency to become nervous and "weepy"; equally insidious was the onset of drenching sweats and readiness to become fatigued. The progression of the latter symptom was rapid and during the month of July the least expenditure of energy seemed to lead to complete exhaustion. The persistence and progression of her symptoms led to the patient's admission to the hospital where she was employed, on August 14, 1935. Full details concerning this admission are lacking but it is said that she was extremely nervous and restless; the drenching sweats continued and the patient became so dehydrated that she voided only at intervals of two or three days. The B.M.R., shortly after admission, was +49. Because the clinical picture exhibited certain features common to hyperthyroidism and pulmonary tuberculosis, these two diseases were considered as diagnostic possibilities. No capsules were taken during her stay in the hospital and she denied having taken any medicines before entering. Later it was decided that this assertion was made in good faith, for she had been entirely unaware of the toxic character of the drug and felt that the infrequent doses that she was taking could have had no bearing on her illness. During a two-weeks sojourn in this hospital, the treatment was restricted to symptomatic therapy, after which she was discharged, unimproved and advised to enter the Johns Hopkins Hospital. Fatigue continued to be her most annoying symptom and having remembered her previous reaction to the "tonic iron capsules," she decided to resort to them again. She took two capsules.

Two days later, on September 8th, 1935, she was admitted to the Johns Hopkins Hospital, exhibiting symptoms of extreme anxiety and nervousness, marked dyspnoea and tachypnoea. During the day of admission, she was nauseated, and vomited several times; she had frequent colliquative night sweats and was unable to void. The salient features noted on physical examination were as follows:—

Temperature, 99.2°. Pulse 110 per minute. Respiratory rate 38 per minute. Blood pressure 100/60. Although there were evidences of recent weight loss, the patient was still slightly over-weight. She was perspiring profusely, was restless and agitated and the respiratory movements were deep and rapid. The skin was flushed but exhibited no yellowish tinge or eruptions. None of the classical eye signs of thyrotoxicosis were present. The thyroid gland was not enlarged or nodular. There was no tremor of the tongue or outstretched fingers. A small peri-rectal abscess which had been incised two days previously was now draining freely. There were no other physical abnormalities.

Laboratory studies included: R.B.C., 5,670,000; Hg, 130%; W.B.C., 11,550. Differential count approximately normal. N.P.N., 48 mgm.%. B.M.R., +104. Blood sugar, 105 mgm.%. Wassermann reaction negative. Sedimentation rate (corrected), 6 mm. per hour. Blood cholesterol, 332 mgm.%. Blood culture negative. E.K.G. normal in every respect except for tachycardia.

In spite of leading questions, the patient persistently denied having taken any drugs prior to her admission and three days elapsed before repeated cross examina-

tions elicited the fact that she had been taking, what she supposed to be, a tonic. Samples of these capsules were obtained and were recognized immediately as having an appearance suggesting dinitrophenol capsules. Chemical analysis of the material contained in them corroborated this assumption and established the content of dinitrophenol as approximately 100 mgm. per capsule.

During the three days following admission, the symptoms increased in severity. Therapy was limited to simple sedatives and the intravenous administration of glucose and salt solution. The temperature rose to 102°; pulse rate to 150 per minute and the B.M.R. reached a maximum of +171. The patient was constipated and could not void; catheterization yielded only small amounts of highly concentrated urine of specific gravity 1.030, containing traces of albumin and sugar but no microscopic pathological elements. Tests of the urine for dinitrophenol were positive. The severity of the symptoms increased until the third day, after which a gradual improvement began. The sweats became less profuse, the vomiting ceased, the symptoms of dehydration disappeared and the restlessness and anxiety diminished. Temperature, pulse and respiration gradually returned to normal. With a steadily increasing output of urine, the N.P.N. became normal. The B.M.R. underwent a striking decline, reaching −9 one week after admission. Ultimate recovery was complicated by the development of a cystitis, which might well have been the result of the frequent catheterizations. Culture of the urine revealed a growth of alpha and beta streptococci. Dinitrophenol was found to be excreted in the urine for eleven days following admission, after which its presence could no longer be demonstrated. At the time of her discharge on September 28, the recovery of the patient was apparently complete. Later she supplied the information, now probably accurate, which indicated that she had taken approximately 152 capsules of dinitrophenol during the period between November 1933 and July 1935.

The patient has returned to the hospital once a month for a basal metabolic rate determination and a careful examination of the eyes. The basal metabolic rates have ranged between −15 and −18. Four months after her discharge she appears to be perfectly well and no opacities have appeared in the lenses or corneae of the eyes. As far as can be determined, there have been no serious aftermaths of any sort.

COMMENT

A review of the literature on the subject indicates that the metabolic rate determination, mentioned above, is the highest recorded in any case of dinitrophenol poisoning. Cases have been reported in which the symptoms were so fulminating that it was impossible to obtain a metabolic rate determination before death occurred (1). In these cases, it was thought that the metabolic rates sometimes had reached +300, but there were no records taken to substantiate such an assumption (2).

If we assume that the history of the case presented here is correct, it becomes difficult to explain the variation in response to the dinitrophenol. After taking the drug with impunity for one and a half years, the patient suddenly developed severe toxic symptoms even though the dose of the drug had not been altered. Statements in the literature indicate that various bizarre effects may follow the administration of this drug. Nadler (3) suggests that it may induce a "delayed poisoning." Imerman presents a case which developed severe symptoms, after the drug had been taken for one year with impunity. Masserman and Goldsmith (5) mention a case which presented evidences of "cumulative toxic effects." It is possible that our case may be such an instance of altered response to dinitrophenol.

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POOLE AND HAINING: *ibid.*, **102,** 1141, (April 7, 1934).
(2) TAINTER: Personal communication.
(3) NADLER: J. A. M. A., **105,** 12, (July 6, 1935).
(4) IMERMAN: *ibid.*, **106,** 1085, (March 28, 1936).
(5) MASSERMAN AND GOLDSMITH: *ibid.*, **102,** 522 (July 15, 1933).

BOOK REVIEWS

(These reviews represent the individual opinions of the reviewers and not necessarily those of the members of the Editorial Board of this journal.)

Clinical Psychiatry. By EDWARD A. STRECKER and FRANKLIN G. EBAUGH. 4th edition. 705 pp. illus. 1935. $5.00. (*P. Blakiston's Son and Company, Philadelphia, Pa.*)

The fourth edition of the textbook by Strecker and Ebaugh is abreast of the times. The introductory chapter on psychobiological conceptions has been enlarged, and references are made to the later contributions of Adolf Meyer. His genetic dynamic concept remains the basis for the special approach of the authors. The chapters dealing with organic psychoses, delirious and schizophrenic reaction types, have been most extensively revised and the newer literature has been summarized and included. A new chapter on the psychopathological problems of childhood by Dr. Leo Kanner contains a summary of the material as it is organized in Dr. Kanner's textbook on child psychiatry and constitutes a useful addition.

This new edition would seem definitely to extend the usefulness of a textbook which has already proved itself of the greatest value to the student of psychiatry. In the next edition, which is bound to come soon, one would like to see the basic principles of psychobiology carried into the whole presentation, instead of too close an adherence to the traditional splitting up of the cases and of the diseases. The present edition offers a rich and informative mass of clinical cases.

T. A. C. R.

The Patient and the Weather, Vol. 1, Part 1, The Footprint of Asclepius. By WILLIAM F. PETERSEN. 127 pp. Illus. $3.75. (*Edwards Brothers, Ann Arbor, Mich., 1935.*)

After a historical review of the different approaches to medical problems and an interesting discussion of the work of Hippocrates, the author presents maps which are taken from the U. S. Draft statistics. He stresses the "storm tracks" in America, and the regional distribution and racial differentiation of diseases.

O. D.

BOOKS RECEIVED

Diseases of the Thyroid Gland. By ARTHUR E. HERTZLER. 3rd ed. rev. 348 pp. illus. $7.50. C. V. Mosby Co., St. Louis, 1935.

The Parathyroids in Health and in Disease. By DAVID H. SHELLING. 335 pp. illus. $6.00. C. V. Mosby Co., St. Louis, 1935.

Lobar Pneumonia and Serum Therapy. By FREDERICK T. LORD and RODERICK HEFFRON. 91 pp. $1.00. The Commonwealth Fund, New York, 1936.

The Diagnosis and Treatment of Diseases of the Peripheral Arteries. By SAUL S. SAMUELS. 260 pp. illus. $3.50. Oxford University Press. New York, 1936.

Le Sang des Hypertendus. By GEORGES CARRIÈRE & CLAUDE HURIEZ. 386 pp. G. Doin & Cie., Paris, 1936.

Enfermedades por infección de las amigdalas. By RAFAEL ROMERO RODRIGUEZ. 165 pp. unbound, 7 pesetas. Imprenta de la Divina Pastora, Seville, 1935.

Synopsis of Clinical Laboratory Methods. By W. E. BRAY. 324 pp. illus. $3.75. C. V. Mosby Co., St. Louis, 1936.

Medical Mycology. By CARROLL WILLIAM DODGE. 900 pp. illus. $10.00. C. V. Mosby Co., St. Louis, 1935.

Examination of the Patient and Symptomatic Diagnosis. By JOHN WATTS MURRAY. 2nd ed. 1219 pp. illus. $10.00. C. V. Mosby Co., St. Louis, 1936.

Abortion, spontaneous and induced. By FREDERICK J. TAUSSIG. 536 pp. illus. $7.50. C. V. Mosby Co., St. Louis, 1936.